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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/807,172	07/03/2002	Leo Gerardus Joseph Frenken	056159-5041	2740

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EXAMINER	
DIBRINO, MARIANNE NMN	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 09/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/807,172	FRENKEN ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4/10/01 & 6/27/05*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *5-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/31/2002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

800

DETAILED ACTION

1. Applicant is required under 37 C.F.R. 1.821(d) to amend the specification to list the appropriate SEQ ID NOS for sequences disclosed in the specification (for example, page 15 at line 20 and Table 2 on page 20).

2. Applicant's amendments filed 4/10/01 and 6/27/05 are acknowledged and have been entered.

3. Applicant's election with traverse of Group I (claims 1-4), and species of SEQ ID NO: 2 in Applicant's amendment filed 6/27/05 are acknowledged.

The basis for Applicant's traversal is of record on page 5 of the said amendment, and briefly is that MPEP 803.04 states that in most cases up to ten sequences will be examined in a single application without restriction, that claim 4 currently recites three sequences, and that this number is a reasonable number for examination purposes.

Applicant's arguments have been fully considered, but are not persuasive for the following reasons.

It is the Examiner's position that the restriction of peptide sequences in claim 4 is a species restriction, not a group restriction for separate inventions. It is the Examiner's further position MPEP 803.04 is directed to searching nucleic acid sequences in one application, and is permissive and not directive. One sequence falls in the range of up to ten sequences. Applicant is reminded that upon a search of the elected peptide species, if it is found to be free of the art, the search will be extended to include another species.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-4 are currently being examined.

Upon consideration of the prior art, the search has been extended to include SEQ ID NO: 3 and 4 recited in instant claim 4.

Accordingly, claims 5-14 (non-elected groups II and III) are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

4. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP 602.01 and 602.02.

The oath or declaration is defective because: Inventor Frenken has not initialed and dated changes to his signature.

5. The disclosure is objected to because of the following informalities:

a. There is no disclosure of SEQ ID NO for the Brief Description of the Drawings for Figures 1, 2 and 4.

b. Claim 4 is objected to because there is no recitation of SEQ ID NO for sequences in the claim.

Appropriate correction(s) is/are required.

6. Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the Applicant had possession at the time of invention of the claimed composition recited in the instant claims.

The instant claims encompass: (1) a method of linking binding units in *any* multivalent binding protein comprising linking said binding units with a polypeptide linking group the amino acid sequence of which group confers restricted conformational flexibility and said linker may by *any* length (*i.e.,* the recitation of "comprise" in dependent claims 2 and 3) and of undisclosed or partially disclosed sequence, (2) the said method wherein the linker "*comprises*" one of SEQ ID NO: 2-4 recited in instant claim 4 and can be any length, and the protein is *any* multivalent binding protein. There is insufficient disclosure in the specification on such a method.

The specification discloses that a "multivalent binding protein" is a protein that has more than one binding unit which allow for specific binding with a molecule partner in a binding pair, and that examples of suitable binding units include antigen binding domains of antibodies, binding domains of receptors such as hormone receptors, lectins, enzymes, and cell adhesion molecules (page 3 at lines 30-36). The specification further discloses that "restricted conformational flexibility" relates to restriction of movement of the antigen binding units about the backbone of the intervening polypeptide linker group, but does not disclose how much restriction of movement corresponds to "restricted conformational flexibility" (page 4 at lines 30-32). The specification does not disclose the definition of "restricted conformational flexibility" for any other multivalent binding protein except for antibodies. The specification exemplifies linking llama antibodies using one of SEQ ID NO: 1-5. The specification does not disclose the structure function relationship between the sequence and length of the linker and the sequence or identity of the multivalent binding protein that is sufficient to confer "restricted conformational flexibility".

The instant disclosure does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera. Since the disclosure fails to provide sufficient relevant identifying characteristics, and because the genus is highly variant, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus as broadly claimed.

7. Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not disclose how to make and/or use the instant invention, a method of linking binding units in a multivalent binding protein comprising linking said binding units with a polypeptide linking group, the amino acid sequence of which group, including the linkers recited in dependent claims 2-4, confers restricted conformational flexibility.

The specification has not enabled the breadth of the claimed invention because the claims encompass: (1) a method of linking binding units in *any* multivalent binding protein comprising linking said binding units with a polypeptide linking group, the amino acid sequence of which group confers restricted conformational flexibility, and said linker may by *any* length (*i.e.,* the recitation of "comprise" in dependent claims 2 and 3) and of undisclosed or partially disclosed sequence, (2) the said method wherein the linker "*comprises*" one of SEQ ID NO: 2-4 recited in instant claim 4 and can be of any length and flanking sequence and the protein is *any* multivalent binding protein, with the exception of (a) the method of claim 4 wherein the multivalent binding protein is an antibody comprised of antigen binding units or is CBHI, and the linking peptide is one of SEQ ID NO: 2-4 or the natural linking peptide from CHBI comprising SEQ ID NO: 4, or

(b) the multivalent binding protein is not an antibody or CHBI and the 28-mer natural linking peptide from CHBI comprising SEQ ID NO: 4 is the linker. There is insufficient disclosure in the specification on such a method. The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the claimed method can be used.

The specification discloses that a "multivalent binding protein" is a protein that has more than one binding unit which allow for specific binding with a molecule partner in a binding pair, and that examples of suitable binding units include antigen binding domains of antibodies, binding domains of receptors such as hormone receptors, lectins, enzymes, and cell adhesion molecules (page 3 at lines 30-36). The specification further discloses that "restricted conformational flexibility" relates to restriction of movement of the antigen binding units about the backbone of the intervening polypeptide linker group, but does not disclose how much restriction of movement corresponds to "restricted conformational flexibility" (page 4 at lines 30-32). The specification does not disclose the definition of "restricted conformational flexibility" for any other multivalent binding protein except for antibodies. The specification exemplifies linking llama antibodies using one of SEQ ID NO: 1-5. The specification does not disclose the structure function relationship between the sequence and length of the linker and the sequence of the multivalent binding protein that is sufficient to confer "restricted conformational flexibility".

Evidentiary reference Alfthan *et al* (Protein Eng. 1995, 8(7): 725-731, IDS reference) teaches that proteolytically stable and flexible linker peptides are needed to join domains in various fusion proteins constructed by protein engineering, that the interdomain linker peptides of natural multidomain proteins provide an ample source of potential linkers for novel fusion proteins. Alfthan *et al* further teach that although these linkers are compatible with the original protein and provide the conformation, flexibility and stability needed for its biological function in its natural environment, they may not be ideally suited for other proteins (especially first paragraph of the Discussion section). Alfthan *et al* further teach a method of making bivalent or higher order valency antibodies comprising linking VH and VL, two binding units in a multivalent binding protein, using the linking peptide ATTGSSPGPT (SEQ ID NO: 4 of instant claim 4), peptides comprising SEQ ID NO: 4 such as PGGNAGTTTTRRPATTGSSPGPTQSHY, or other proline containing polypeptides, *i.e.,* what they consider "flexible" linker peptides from CBHI.

It is noted by the Examiner that the instant specification discloses that peptide linking groups from naturally occurring proteins such as CBHI serve to restrict conformational flexibility, and the ATTGSSPGPT comes from CBHI (especially page 8 at lines 27-33 and page 9 at line 14).

There is insufficient guidance in the specification as to how to make and/or use instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite in the recitation of "confers restricted conformational flexibility" because it is not clear what is meant, *i.e.*, what the metes and bounds of the limitation are, what degree of restriction of movement is encompassed.

10. For the purpose of prior art rejections, the filing date of the instant claims 1-4 is deemed to be the filing date of the 99303008.6 foreign priority document, *i.e.* 4/22/99, as the 9806991 document does not support the claimed limitation "multivalent binding protein" in the context of the method recited in the instant claims. Only "multivalent antigen binding protein" is recited in the 9806991 document.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. During patent examination, the pending claims must be "given the broadest reasonable interpretation consistent with the specification." Applicant always has the opportunity to amend the claims during prosecution and broad interpretation by the examiner reduces the possibility that the claim, once issued, will be interpreted more broadly than is justified. In re Prater, 162 USPQ 541, 550 - 51 (CCPA 1969).

With regard to the limitation "confers restricted conformational flexibility" recited in claim 1, the specification discloses that "restricted conformational flexibility" relates to restriction of movement of the antigen binding units about the backbone of the intervening polypeptide linker group, but does not disclose how much restriction of movement corresponds to "restricted conformational flexibility" (page 4 at lines 30-32). The specification does not disclose the definition of "restricted conformational flexibility" for any other multivalent binding protein except for antibodies. The specification does not disclose the structure function relationship between the sequence and length of the linker and the sequence or identity of the multivalent binding protein that is sufficient to

confer "restricted conformational flexibility". Therefore the claims are being interpreted to include polypeptide linkers that confer some degree of restricted conformational flexibility, *i.e.,* they contain predominantly amino acid residues other than alanine and/or glycine.

13. Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Alfthan *et al* (Protein Eng. 1995, 8(7): 725-731, IDS reference).

Alfthan *et al* teach a method of making bivalent or higher order valency antibodys comprising linking VH and VL, two binding units in a multivalent binding protein, using the linking peptide ATTGSSPGPT (SEQ ID NO: 4 of instant claim 4). Alfthan *et al* further teach using a peptide comprising ATTGSSPGPT as a linker peptide in the same way, and teach using linkers up to 30 amino acid residues in length. Alfthan *et al* teach the use of a number of proline-containing (inflexible) linkers (see entire reference, especially abstract, first full paragraph at column 2 on page 725, paragraph spanning pages 725-726, Figure 1A).

14. Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Srisodsuk *et al* (J. Biol. Chem. 1993, 268(28): 20756-20761, IDS reference).

Srisodsuk *et al* teach using a peptide comprising ATTGSSPGPT (SEQ ID NO: 4 of instant claim 4), the peptide TTTRRP**ATTGSSPGPT**, to link binding units, or domains, in a multivalent binding protein CBHI.

15. Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 93/02198 A1 (IDS reference).

WO 93/02198 A1 teaches linking a variety of functional proteins or protein domains, such as antigen binding domains, using linking polypeptides such as those from naturally secreted multidomain proteins. WO 93/02198 A1 teaches that more than two protein domains or regions may be joined, for example, four immunoglobulin domains linked to a single polypeptide via three linkers, or double scFv antibodies. WO 93/02198 A1 teaches that these linkers contain mainly Pro, Thr and or Ser with occasional Ala, Cys, Gly, Gln or charged amino acid residues (especially page 13 at line 10 through page 17at line 21, claims). WO 93/02198 A1 teaches use of a linker comprising SEQ ID NO: 4 of instant claim 4, *i.e.,* ATTTGSSPGPT, said linker being 28 amino acid residues in length for linking any protein or protein subunit, but exemplified for joining antigen binding units of single chain antibodies (especially Figure 2, Figure 2 legend), as well as linkers consisting of Ser, Thr and Gly residues only (especially paragraph spanning pages 4-5). WO 93/02198 A1 teaches using polypeptide linkers from bacterial multidomain proteins are about 20-30 amino acid residues in length (especially page 5 at the last paragraph).

16. No claim is allowed.

17. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware of in the specification.

18. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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